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Case Report

Familial Paraganglioma Presenting With Acute Coronary Syndrome and Coronary Vasospasm

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Abstract

Familial paraganglioma syndrome (FPS) is a rare genetic disorder characterized by the development of paragangliomas (PGLs) and pheochromocytomas (PCCs). Here, we describe the case of a 42-year-old man with a family history of FPS, who presented with episodic chest pain and was diagnosed with acute coronary syndrome secondary to cardiac PGL-induced vasospasm. A thorough review of the family history confirmed several cases of PGLs and PCCs in the immediate family circle. A pathogenic variant in the succinate dehydrogenase (*SDH*) gene was revealed, elucidating the hereditary nature of the condition. Subsequent gallium (^{68}Ga)-edotreotide positron emission tomography confirmed the presence of multiple lesions with increased uptake consistent with PGLs, including 2 primary cardiac PGLs that may have accounted for a coronary vasospasm due to the secretion of catecholamines.

Key Words: familial paraganglioma syndrome, vasospasm, cardiac paraganglioma

Abbreviations: ^{68}Ga, gallium; ACS, acute coronary syndrome; CS, coronary sinus; CT, computed tomography; ECG, electrocardiogram; FPS, familial paraganglioma syndrome; MRI, magnetic resonance imaging; NR, normal range; PB, peripheral blood; PCCs, pheochromocytomas; PET, positron emission tomography; PGLs, paragangliomas; *SDH*, succinate dehydrogenase gene; SSA, somatostatin analogue.

Introduction

Familial paraganglioma syndrome (FPS) is an autosomal dominant disorder characterized by the development of paragangliomas (PGLs) and pheochromocytomas (PCCs), originating from neural crest-derived chromaffin cells. Sympathetic PGLs, usually catecholamine-secreting, arise in the paravertebral ganglia of the thorax, abdomen, and pelvis. In contrast, most parasympathetic PGLs are nonfunctional and located along the glossopharyngeal and vagus nerves in the neck and skull base. Thus, while FPS patients may exhibit diverse clinical manifestations, cervical PGLs typically do not cause catecholamine-related symptoms [1]. FPS is often associated with mutations in genes encoding subunits of the succinate dehydrogenase (SDH) enzyme complex, such as *SDHB*, *SDHC*, and *SDHD* [1, 2]. Here, we describe a unique case of FPS presenting as acute coronary syndrome (ACS), potentially influenced by PGL-induced vasospasm in the setting of underlying coronary artery disease. This report highlights our diagnostic approach in identifying multifocal and functional cardiac PGLs.

Case Presentation

A 42-year-old man presented to the emergency department with episodic chest pain. The patient's symptoms included recurrent episodes of chest pain, each of short duration and unrelated to effort, which had persisted for the past 2 years. These episodes were described as pressure-like pain in the central chest, lasting for a few minutes, and resolving spontaneously. The patient had not sought medical attention until recently, when he experienced an episode of intense pressure-like chest pain at rest. This episode was associated with transient subepicardial ischemic changes on electrocardiogram (ECG), including ST-segment elevation in the inferior and posterior leads.

The patient had multiple cardiovascular risk factors, including tobacco use, dyslipidemia, obesity (body mass index: 30.1), and a history of severe alcohol dependence. He was also diagnosed with obsessive-compulsive disorder, for which he was receiving treatment with clomipramine and aripiprazole. Additionally, the patient had a history of bilateral cervical masses, for which he had previously declined further investigation.

Diagnostic Assessment

An urgent coronary angiography revealed single-vessel disease, with a severe lesion in the mid third of the circumflex artery at the bifurcation with the first obtuse marginal branch, for which a drug-eluting stent was successfully implanted. No other significant lesions were observed but, during the angiography, injections into the right coronary artery revealed a well-defined vascular image, in the vicinity of the right coronary artery and not communicating with the right ventricular cavity.

A thorough clinical evaluation, including directed questioning, revealed a substantial family history of FPS, with multiple

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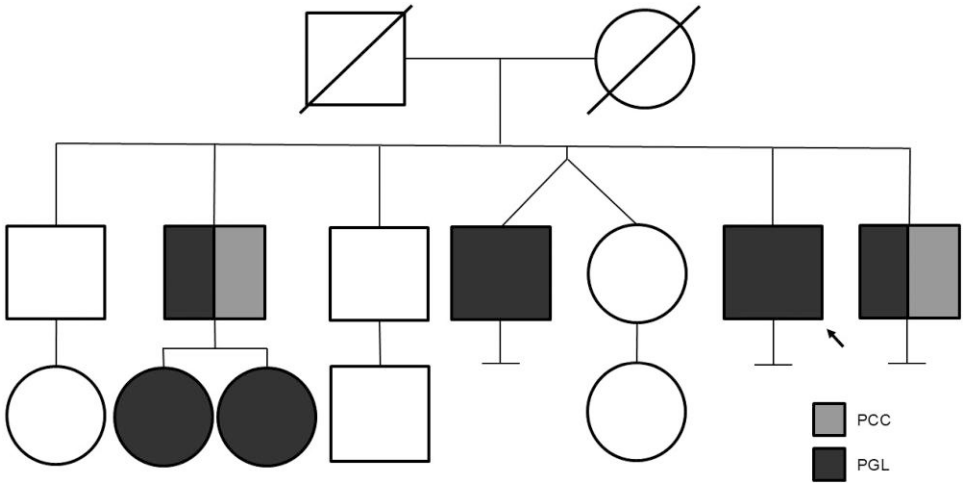

Figure 1. The figure shows the genealogical tree of our patient, with the respective endocrinological history of each individual.
Abbreviations: PCC, pheochromocytoma; PGL, paraganglioma.

cases of PGLs and PCCs among first- and second-degree relatives. Fig. 1 shows a first-degree family history, with several cases of PGLs and PCCs reported. One of the patient's brothers had been previously diagnosed with FPS, harboring a pathogenic variant in the *SDHD* gene (deletion of 4 nucleotides at positions 337 to 340 of GAT [p.Asp113Metfsx21] in heterozygosis at the fourth exon of the *SDHD* gene).

During hospitalization, the patient experienced 2 brief episodes similar to those he had been experiencing for years, both brief and associated with transient ST-segment elevation in the inferior leads, as documented on ECG (Fig. 2). One episode was successfully relieved with sublingual nitroglycerin, while the other resolved spontaneously. A follow-up ECG, performed after symptom resolution, showed normalization of repolarization (see Fig. 2). According to classic coronary anatomy, these transient ECG changes did not appear to be explained by the artery treated during angioplasty and were instead associated with episodes of vasospasm.

Subsequently, a comprehensive computed tomography (CT) revealed the presence both of cervical and cardiac PGLs. The carotid body PGLs appeared as rounded and homogeneous lesions with marked contrast enhancement at the bifurcation of both carotid arteries. Additionally, 2 highly vascularized cardiac lesions, suspicious for cardiac PGL, were identified: 1 in the distal segment of the right coronary artery, and the other in the posterior atrial branch of the left atrium, measuring 14 × 17 mm and 4 × 8 mm in diameter, respectively. Fig. 3 shows a transverse section of the cardiac CT, depicting the largest PGL located in the distal segment of the right coronary artery.

Laboratory studies showed elevated plasma normetanephrine levels of 648 pg/mL (3303 pmol/L) (normal range [NR] = <216 pg/mL; < 1101 pmol/L), norepinephrine levels of 1022 pg/mL (6042 pmol/L) (NR = 135-300 pg/mL; 798-1773 pmol/L), and dopamine levels of 177 pg/mL (1156 pmol/L) (NR = 10-150 pg/mL; 65-979 pmol/L), supporting the presence of functional PGLs. Plasma metanephrine and epinephrine levels were within the normal range.

To further characterize the lesions, gallium (^{68}Ga)-edotreotide positron emission tomography (PET)/CT imaging was performed, revealing multiple lesions with intensely increased uptake (Fig. 4). These lesions were located bilaterally at the carotid level, as well as within the pericardial region, in contact with the circumflex artery, adjacent to the anterolateral left atrium, and in the distal segment of the right coronary artery, supporting the presence of cardiac PGLs.

Further evaluation, after hospital discharge, included simultaneous measurements of plasma fractionated metanephrines and catecholamines in the coronary sinus (CS) and peripheral blood (PB). Our multidisciplinary team decided to perform CS sampling to obtain direct biochemical evidence of catecholamine secretion from the cardiac PGLs. Although this technique is not routinely used for cardiac PGLs, we deemed it appropriate in this case to guide potential surgical intervention and provide the patient with a stronger rationale for definitive treatment. Nonetheless, we emphasize that the decision to perform CS sampling must be made on a case-by-case basis, carefully balancing the potential diagnostic benefits against the inherent procedural risks. These tests revealed elevated norepinephrine and dopamine concentrations, with a sinus-to-peripheral gradient greater than 2:1, reinforcing the hypothesis of cardiac PGL-induced vasospasm contributing to the patient's angina. To minimize potential interference with the measurements, clomipramine was discontinued a few days before the procedure. Table 1 shows the laboratory results of plasma fractionated metanephrines and catecholamines obtained simultaneously from the CS and PB. Despite elevated norepinephrine and dopamine levels, normal normetanephrines levels were observed, likely due to the acute release of catecholamines triggered by the angiographic procedure, suggesting a direct response from the cardiac PGLs. Additionally, genetic testing confirmed the presence of the same *SDHD* gene pathogenic variant identified in the patient's brother. This pathogenic variant has been previously reported and is available in the ClinVar database under accession number RCV000007321.12.

Treatment

Treatment with α-blockers (doxazosin 4 mg twice daily) was initiated with the diagnostic hypothesis of transient coronary vasospasm triggered by potential catecholamine surges from cardiac PGLs. Since the initiation of the α blockade, the patient's blood pressure has remained between 110 and 130/70 and 95 mm Hg, with no symptoms of angina.

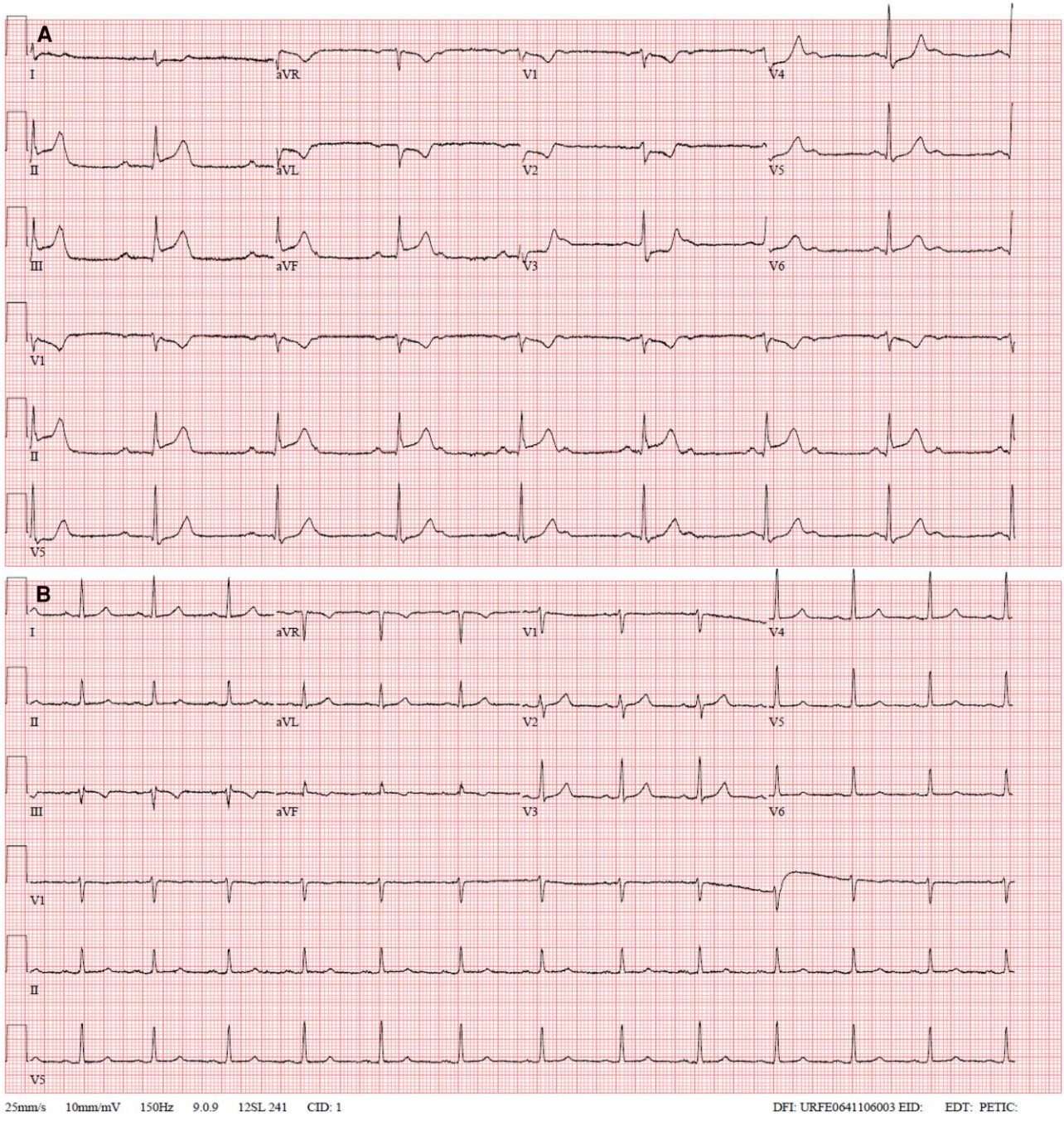

Figure 2. Electrocardiographic findings during and after the chest pain episode. A, ECG recorded during chest pain, showing 2:1 atrioventricular block and ST-segment elevation in the inferior and posterior leads, with reciprocal ST-segment depression in the high lateral leads, indicative of subepicardial injury. B, ECG after resolution of chest pain, showing no repolarization abnormalities.

Abbreviation: ECG, electrocardiogram.

Outcome and Follow-up

At an outpatient review, surgical intervention for the PGLs was proposed, but the patient declined any type of surgery. At 1-year follow-up, a cardiac CT and a ^{68}Ga-edotreotide PET/CT were performed, both showing stability of the cardiac and carotid body PGLs, with no new lesions detected. The patient once again declined cardiac surgery but agreed to undergo surgery for the carotid body PGLs, due to compressive symptoms.

Discussion

PCCs are chromaffin cell tumors of the adrenal medulla, typically associated with catecholamine excess. PGLs originate from extra-adrenal chromaffin tissue and may be either hormonally active or inactive. Approximately 1% to 2% of PGLs are located in the chest, with an even smaller subset originating as primary cardiac tumors, making primary cardiac PGL an exceptionally rare condition [3]. Approximately 75% of cardiac PGLs arise spontaneously, whereas 25%

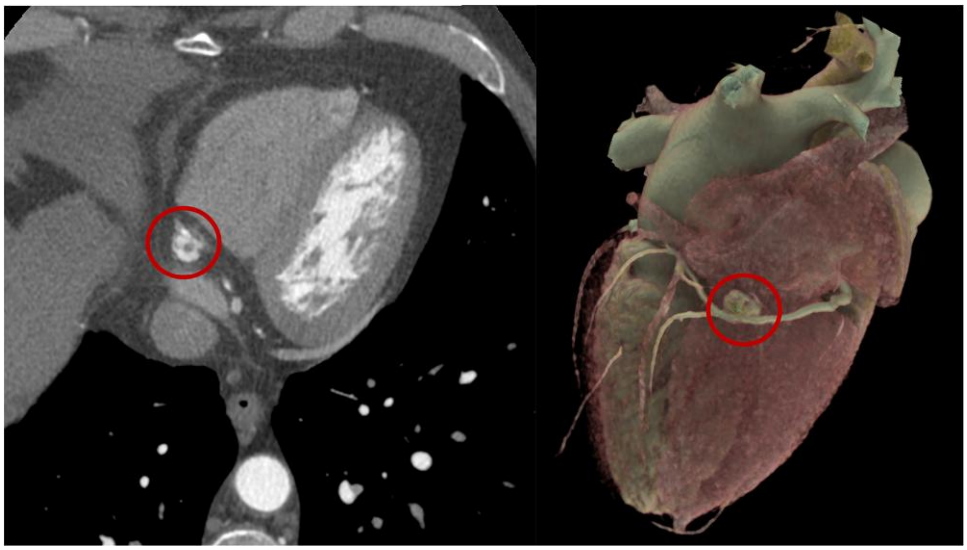

Figure 3. The image on the left shows a transverse section view of the cardiac CT, depicting the largest PGL located in the distal segment of the right coronary artery (indicated by the circle). On the right, a volumetric reconstruction is displayed.

Abbreviations: CT, computed tomography; PGL, paraganglioma.

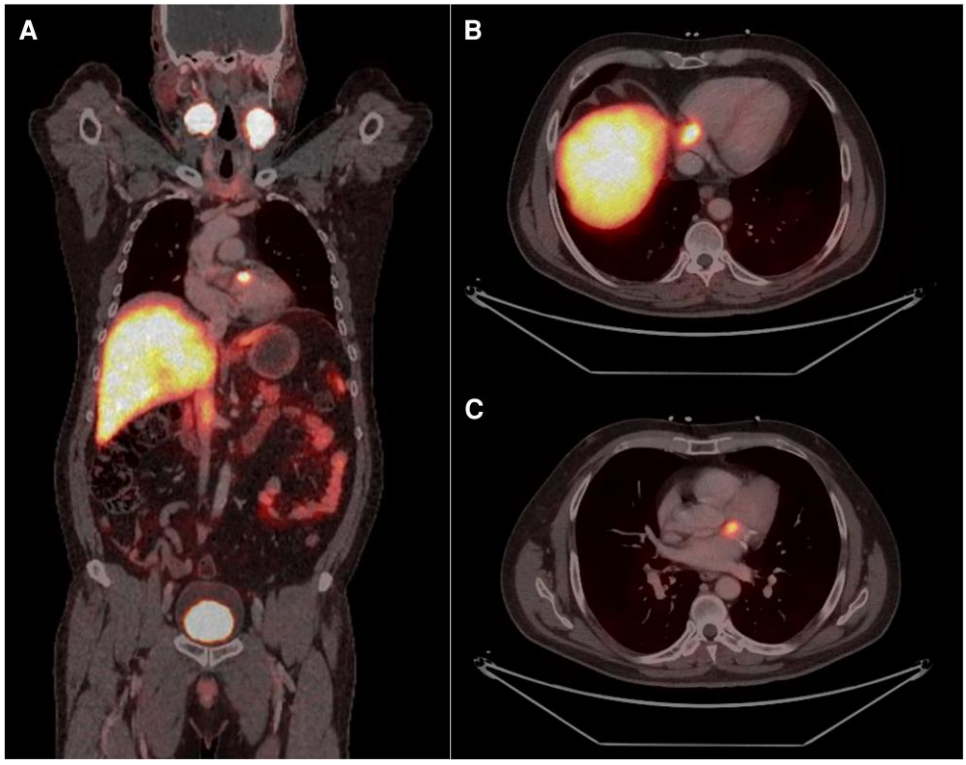

Figure 4. The images obtained in the gallium (^{68}Ga)-edotreotide PET/CT study are shown. A, Lesions located at the bifurcation of both common carotid related to bilateral carotid PGLs. B and C, In the chest, focal areas of increased uptake are shown in the right coronary sulcus, B, at the distal segment of the right coronary artery, and another, C, in contact with the adjacent circumflex artery anterolateral to the left atrium, both suggestive of cardiac PGLs.

Abbreviations: CT, computed tomography; PET, positron emission tomography; PGL, paraganglioma.

have genetic associations [4]. According to some authors, the left atrium is the most common site of origin [5, 6], followed by the right atrium. Most cases are located within the pericardium, with intracardiac location being less frequent [5].

Although these manifestations are not specific to cardiac PGLs, hormonally active cases typically present with catecholamine-related symptoms: hypertension, anxiety, sweating, and/or palpitations. In a review of 158 patients with cardiac PGLs, chest pain was reported in 27 cases (18.0%) [7], possibly mimicking angina with paroxysmal episodes. Another case report described a cardiac PGL presenting as heart failure with a severely reduced left ventricular ejection fraction [8].

Table 1. Laboratory results of plasma metanephrines and catecholamines simultaneously obtained from coronary sinus and peripheral blood

Biochemical parameter	CS	PB	Normal range
Metanephrine	91 pg/mL (505 pmol/L)	30 pg/mL (166 pmol/L)	<100 pg/mL (<555 pmol/L)
Normetanephrine	186 pg/mL (948 pmol/L)	151 pg/mL (770 pmol/L)	<216 pg/mL (<1101 pmol/L)
Norepinephrine	**932 pg/mL (5509 pmol/L)**	**461 pg/mL (2725 pmol/L)**	135-300 pg/mL (798-1773 pmol/L)
Epinephrine	52 pg/mL (284 pmol/L)	19 pg/mL (104 pmol/L)	20-60 pg/mL (109-328 pmol/L)
Dopamine	**212 pg/mL (1384 pmol/L)**	90 pg/mL (588 pmol/L)	10-150 pg/mL (65-979 pmol/L)

Abnormal values are shown in bold font. Values in parenthesis are International System of Units (SI).
Abbreviations: CS, coronary sinus; PB, peripheral blood.

For the diagnosis of cardiac PGLs, magnetic resonance imaging (MRI) and CT provide essential anatomical details and assess tumor relations with surrounding structures [5]. However, due to their rarity, diagnosis based solely on these imaging methods can be challenging. Functional imaging, particularly receptor-based strategies using PET, complements structural imaging by confirming somatostatin receptor expression and aiding in lesion characterization, although it may have suboptimal spatial resolution. Therefore, a combined approach is recommended for an accurate diagnosis. Furthermore, coronary angiography plays a crucial role in the preoperative diagnosis by delineating the vascular supply of the lesion and identifying any involvement of the coronary arteries, which is essential for planning a safe and effective surgical approach [7]. Determining the secretory phenotype is essential, and the pharmacological approach primarily using α-adrenergic receptor blockers (with doxazosin or phenoxybenzamine being the most frequently used) remains the cornerstone of medical treatment for hormonally active PGLs [1, 9].

Although complete surgical excision remains the primary treatment approach, the highly vascular and nonencapsulated nature of these tumors could pose a considerable challenge for surgical resection, and some cases may be deemed inoperable [10]. Preresection embolization has been documented as a treatment option for cardiac PGL [11]. However, its use remains infrequent due to the substantial risk of catecholamine surges. A recent study highlighted favorable mortality rates and long-term survival in 19 cases of cardiac PGLs at a single center [6]. Despite the rarity of the tumor and limited surgical experience, the study reported successful management and outcomes achieved by a multidisciplinary cardiac tumor team. The operative mortality rate was 10.6% with survival rates of 88.2%, 71.8%, and 71.8% at 1, 5, and 10 years post surgery, respectively [6]. In another review of 82 cases, an excellent long-term prognosis was reported for patients who underwent complete surgical removal of the PGL. The only determinants of mortality were intracardiac location and the development of metastasis with a mean follow-up period of 17 months [5].

In addition to surgical and interventional approaches, somatostatin analogues (SSAs) have emerged as a potential strategy for managing certain PGLs by controlling tumor growth and hormone secretion [12]. SSAs mimic somatostatin, by binding to receptors on neuroendocrine tumors, thereby inhibiting catecholamine release. Nevertheless, the efficacy of SSAs in treating cardiac PGLs is limited. Lutetium (^{177}Lu)-DOTATATE–based radionuclide therapy has been proposed for slowly progressive PGLs; however, its role in cardiac PGLs remains uncertain due to limited clinical experience and the potential risk of triggering catecholamine secretion. Additionally, cabozantinib, a multityrosine kinase inhibitor, can be used when PGLs cannot be treated surgically and has shown effectiveness in treating an unresectable cardiac PGL, as reported in a case study [13].

The diagnosis of FPS requires a multidisciplinary approach and tailored management strategies. Our case contributes to the limited pool of reported cases of multiple primary cardiac PGLs, and illustrates a rare presentation of FPS with ACS, probably resulting from PGL-induced vasospasm. This association highlights the need for comprehensive cardiovascular evaluation in patients with known or suspected FPS.

Learning Points

- Cardiac PGLs can mimic ACS, underscoring the importance of a high index of suspicion in patients with FPS who present with chest pain and dynamic ECG changes.
- Functional imaging with ^{68}Ga-edotreotide PET/CT is crucial for identifying multifocal PGLs. However, its suboptimal spatial resolution necessitates complementary MRI or CT for precise localization.
- CS catheterization can be considered on a case-by-case basis for direct measurement of catecholamines and their metabolites. In selected cases of cardiac PGLs, such measurements may help confirm tumor functionality and guide decisions regarding surgical intervention or alternative management strategies.

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Contributors

All authors made individual contributions to authorship. C.P.-J., L.G.P., M.-J.B., and A.S.-S. were involved in the

diagnosis and paramount clinical decision-making role of the patient; C.P.-J., L.G.P., V.P., and C.Q. were involved in the literature research, preparation of figures, and manuscript drafting and submission. All authors reviewed and approved the final manuscript.

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Disclosures

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Informed Patient Consent for Publication

Signed informed consent obtained directly from the patient.

Data Availability Statement

Data sharing is not applicable to this article as no data sets were generated or analyzed during the present study.

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